REMARKS

Claims 1, 6 and 8-10 are amended, claims 4, 7 and 12 are canceled, and claims 14-15 are newly added. Upon entry of the claims amendments, claims 1-3, 5-6, 8-11 and 13-15 are pending for continual examination. Claims 1, 6 and 8-10 are amended to specifically define R_1 and R_2 groups in terms of particular protecting groups. Claims 14-15 are directed to specific compounds of formula (IIc) and (IIc') respectively as exemplified in the working examples. The claim amendments find support throughout the specification and do not introduce new matter.

Rejection of claim 8 under 35 U.S.C. §102(b)

Examiner has rejected claim 8 for lack of novelty over U.S. Pat. No. 5,399,578 (the '578 patent). In response, applicant has amended claim 8 by specifically defining R_1 and R_2 groups, such that the scope of claim 8 as amended does not encompass the prior art compound. Therefore, the rejection is overcome.

Rejection of claim 9 under 35 U.S.C. §103(a)

Examiner has rejected claim 9 for being obvious over U.S. Pat. No. 5,399,578 (the '578 patent) on the ground that it would be obvious to substitute the single bond in the prior art compound with a double bond to make the present claimed compound. Applicant does not share the examiner's view. A substitution of a single bond in a compound with a double bond would significantly change the structure of the compound. It is unpredictable as to how a structural change would affect properties/functions of a compound. A change from a single bond to a double bond could ultimately result in substantial property/function changes. Therefore, considering the unpredictability of chemical compounds, it is impossible for one skilled in the art to foresee the impacts of structural changes on the properties/functions of the compound. For example, in Nagase, H. et al., "The pharmacological profile of δ opioid receptor ligands, (+) and (-) TAN-67 on pain modulation," *Life Sciences*, 68: 2227-2231 (2001), the authors have reported that substitution of a methylcyclo-propyl (a cycloalkyl) group with a methyl (an alkyl) group changes the compound from an opioid receptor antagonist to its agonist. See Figure 2a) and 2d) on page 2229 of the article (article enclosed along with the response). Accordingly, it is clearly not obvious to one skilled in the art to substitute the single bond disclosed in the '578 patent with a double bond in order to make the claimed compound.

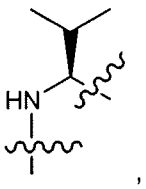
Furthermore, the '578 patent discloses compounds of formula (I) whose structures are substantially different from the claimed compound in the present application, and the synthetic process for making the compounds of formula (I) is substantially different from the one of the

present invention. The relevant compound mentioned by the examiner under this rejection is used as a starting material to react with another compound to make the final compound of formula (I). The synthetic schemes in the '578 patent do not involve forming a double bond at any point. The '578 patent also fails to suggest or imply or provide any reason to one skilled in the art to substitute the single bond with the double bond in connection with making the final compounds of formula (I). To make a claimed compound obvious over a prior art compound, it is necessary to show that prior art has suggested making modifications to get the claimed compound. See *Takeda Chemical Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 2007 WL 1839698 (Fed. Cir. June 28, 2007).

Therefore, based on the above, there is no prima facie case of obviousness to claim 9 over the '578 patent.

Rejection of claims 1-7 and 10-13 under 35 U.S.C. §103(a)

The examiner has rejected claims 1-7 and 10-13 for being obvious over U.S. Pat. No. 5,260,325 (the '325 patent) on the ground that the changes made on the reagents in the present invention are obvious over the prior art process. Applicants respectfully disagree. The examiner has compared tertiary amines of formula I and its precursors in the '325 patent, to the tertiary amines of formula I and its precursors in the present invention. According to the examiner the only structural difference between the compounds described in the '325 patent and the compounds of the present invention is the length of the acyl chain. However, the applicant would like to remark that while the alpha-isopropyl moiety is a main structural element of amines of the present invention, amines in the '325 patent do not embrace any alpha-isopropylamine



because according to the '325 patent, none of the definitions of R_8 comprise an alpha-isopropylamine. Therefore, the '325 patent does not provide one skilled in the art with the motivation to neither use nor synthesize the specific alpha-isopropylamines amines of the present invention.

As regards the reductive amination, the '325 patent (column 12, 1st paragraph) simply makes reference to an alternative method for the preparation of a secondary amine of formula 2, which is structurally related to the amine of formula IIc according to the present invention. The '325 patent neither teaches nor suggests any particular advantage attached to said alternative

preparation of the amine of formula 2. Moreover, it is not clear that it works well at all to provide an amine of formula IIc according to the present invention.

In contrast, the present invention shows several unexpected technical effects:

1. As pointed out on page 8, paragraph 2 (lines 2 and 15) of the specification, the reductive amination, according to the present invention (step a), can be carried out in a solvent or a mixture of solvents including water. The person skill in the art recognizes that such a complete conversion in the presence of water is surprising. The condensation of a primary amine with an aldehyde yields the corresponding imine plus water, thus, one usually drives the reaction to completion by performing the reaction under azeotropical conditions, that is removing water. It is thus surprising that the imine formation step can occur to complete conversion in the presence of water. As indicated on page 10§5, the reductive amination according to the present invention is even most preferably carried out without removal of free water.

2. As explained on page 17 paragraph 2 (line 5) of the specification, the compounds of formula IIc (secondary amine) and IIc' (imine) can surprisingly be obtained in an essentially enantiomerically pure form. Under the basic reaction conditions, at least partial racemisation is expected. However, compounds of formula IIc or IIc' can be obtained in at least 95% enantiomeric excess.

Therefore, the '325 patent does not lead to the subject matter of the present invention, since there is no suggestion/teaching in this document about the particular advantages of a reductive amination method for the preparation of compounds of formula IIc or IIc', in the presence of water and under basic conditions. Thus, a person skilled in the art could not have reasonable expectation that such a preparation method could exhibit unexpected advantageous properties as described on pages of the specification above-mentioned and supported by the experimental part of the specification, and the present invention is not obvious over the '325 patent.

In view of the above, applicant submits that all issues raised in the Office Action have been properly addressed. Applicant respectfully requests withdrawal of the rejections.

Respectfully submitted,

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